

ORIGINAL ARTICLE

Brain Surface Anatomy in Adults With Autism

The Relationship Between Surface Area, Cortical Thickness, and Autistic Symptoms

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Context: Neuroimaging studies of brain anatomy in autism spectrum disorder (ASD) have mostly been based on measures of cortical volume (CV). However, CV is a product of 2 distinct parameters, cortical thickness (CT) and surface area (SA), that in turn have distinct genetic and developmental origins.

Objective: To investigate regional differences in CV, SA, and CT as well as their relationship in a large and well-characterized sample of men with ASD and matched controls.

Design: Multicenter case-control design using quantitative magnetic resonance imaging.

Setting: Medical Research Council UK Autism Imaging Multicentre Study.

Participants: A total of 168 men, 84 diagnosed as having ASD and 84 controls who did not differ significantly in mean (SD) age (26 [7] years vs 28 [6] years, respectively) or full-scale IQ (110 [14] vs 114 [12], respectively).

Main Outcome Measures: Between-group differences in CV, SA, and CT investigated using a spatially unbiased vertex-based approach; the degree of spatial over-

lap between the differences in CT and SA; and their relative contribution to differences in regional CV.

Results: Individuals with ASD differed from controls in all 3 parameters. These mainly consisted of significantly increased CT within frontal lobe regions and reduced SA in the orbitofrontal cortex and posterior cingulum. These differences in CT and SA were paralleled by commensurate differences in CV. The spatially distributed patterns for CT and SA were largely nonoverlapping and shared only about 3% of all significantly different locations on the cerebral surface.

Conclusions: Individuals with ASD have significant differences in CV, but these may be underpinned by (separable) variations in its 2 components, CT and SA. This is of importance because both measures result from distinct developmental pathways that are likely modulated by different neurobiological mechanisms. This finding may provide novel targets for future studies into the etiology of the condition and a new way to fractionate the disorder.

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Group Information: The members of the Medical Research Council UK Autism Imaging Multicentre Study (MRC AIMS) Consortium appear at the end of this article.

AUTISM SPECTRUM DISORDER (ASD) is characterized by a triad of symptoms, namely impaired social communication, deficits in social reciprocity, and repetitive and stereotyped behavior.^{1,2} There is consensus that ASD is a highly genetic neurodevelopmental condition that is accompanied by differences in brain anatomy.

Evidence for neuroanatomical differences in ASD comes from a variety of post-mortem and structural neuroimaging studies (reviewed by Amaral et al³ and Toal et al⁴). For example, differences have been described in the cerebellum,⁵ amygdala-

hippocampal complex,⁶⁻⁹ frontotemporal regions,^{6,7,10} and caudate nucleus.^{11,12} Most of these prior anatomical studies were based on volumetric analyses. However,

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in particular for the cortical volume (CV)—owing to its specific anatomical characteristics—it would be informative for the understanding of the biological basis of ASD to determine whether differences in CV are driven by differences in cortical thickness (CT) or surface area (SA), or a combination of both.

Table 1. Subject Demographic Characteristics

| Characteristic | Mean (SD) [Range] | |
|-------------------------------|---------------------|---------------------|
| | ASD (n = 84) | Control (n = 84) |
| Age, y ^a | 26 (7) [18-43] | 28 (6) [18-43] |
| WASI IQ score ^a | | |
| Full scale | 110 (14) [73-135] | 114 (12) [77-137] |
| Verbal | 109 (14) [77-139] | 109 (14) [71-141] |
| Performance | 108 (16) [73-138] | 116 (12) [76-135] |
| ADI-R score ^b | | |
| Social | 18.04 (5.31) [9-28] | NA |
| Communication | 14.08 (4.29) [8-25] | NA |
| Repetitive behavior | 4.97 (2.16) [2-10] | NA |
| ADOS total score ^c | 9.26 (4.49) [3-21] | NA |

Abbreviations: ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; NA, not applicable; WASI, Wechsler Abbreviated Scale of Intelligence.

^aThere were no significant between-group differences in age, full-scale IQ, or verbal IQ (all $P > .05$, 2-tailed); performance IQ differed significantly between groups ($P = .001$).

^bInformation was available for all 84 subjects with ASD.

^cInformation was available for 82 subjects with ASD.

The existence of such independent variations in CT and SA is potentially of great importance as there is evidence to suggest that they have distinct genetic determinants,¹³ contrasting phylogeny,¹⁴ and differing developmental trajectories.¹⁵ A recent twin study suggests that although both CT and SA are highly heritable, they are unrelated genetically and follow discrete genetic mechanisms.¹³ Also, it has been proposed that measures of CT and SA reflect different aspects of the underlying neural architecture. For instance, it is now widely recognized that the cerebral cortex is organized into ontogenetic columns¹⁶ and that cells within a column share a common origin before migrating to their location within the cortex during development (radial unit hypothesis).^{14,17,18} In this model, the number of cells within cortical columns mediates CT, whereas SA primarily reflects the number of columns within a cortical region.¹⁴ Measurements of CV may therefore reflect structural properties that are unique to cortical SA or unique to CT. Thus, it is necessary to explore CT and SA separately to better understand the neurobiological mechanisms associated with brain abnormalities in ASD and to refine the autism endophenotype for future etiological studies.

To date, relatively few studies have investigated region-specific differences in CT in individuals with ASD, and those that are available reported inconsistent results. In children, some studies report increases in CT of frontotemporal regions,^{19,20} while others note the opposite trend in similar regions.²¹ In adults, most studies report cortical thickening of the frontal cortex,^{22,23} while the temporal lobe may be thicker²² or thinner²⁴ in ASD. To our knowledge, only 2 prior studies on ASD examined CV, SA, and CT in the same sample of individuals. First, a recent study by Hazlett et al²⁵ suggests that increased CV may be associated with increased cortical SA rather than CT. Second, Raznahan et al²⁶ reported altered neurodevelopmental trajectories for CV and CT (also see the articles by Mak-Fan et al¹⁹ and Scheel et al²²), but not SA, in a cross-sectional study of children and adults with ASD. Notably, a differential

growth trajectory for CT and SA has also been reported in neurotypical subjects, in whom frontal SA and CV decrease with increasing age (ages 12-16 years), while frontal CT increases during maturation.²⁷ These prior studies were important first steps toward establishing the specific determinants of volumetric differences in ASD, and they further highlight the need for investigating CT and SA in isolation.

Our aim was to investigate regional differences in CV, SA, and CT as well as their relationship in a large and well-characterized sample of men with ASD and matched controls. We used a spatially unbiased vertex-based approach that provides measures of CV, SA, and CT at several thousand points across the cortical sheet. This allowed us to investigate the following: (1) the spatially distributed networks of differences in CT and SA; (2) the degree of spatial overlap between them; and (3) their relative contribution to observed differences in regional CV. It was hypothesized that individuals with ASD show neuroanatomical differences in predominantly frontotemporal regions and that these differences are associated with the severity of autistic symptoms.

METHODS

PARTICIPANTS

Eighty-four right-handed men with ASD and 84 matched controls aged 18 to 42 years were recruited by advertisement and subsequently assessed at 1 of 3 centers: the Institute of Psychiatry, King's College London; the Autism Research Centre, University of Cambridge; and the Autism Research Group, University of Oxford. Approximately equal ratios of cases to controls were recruited at each site: London, 38:38; Cambridge, 31:29; and Oxford, 15:17.

Exclusion criteria for all participants included a history of major psychiatric disorder, head injury, genetic disorder associated with autism, or any other medical condition affecting brain function. We excluded participants with substance abuse and participants on antipsychotic medications, mood stabilizers, or benzodiazepines. All participants with ASD were diagnosed according to *International Statistical Classification of Diseases, 10th Revision* research criteria and confirmed using the Autism Diagnostic Interview–Revised²⁸ (ADI-R) to ensure that all participants with ASD met the criteria for childhood autism. All cases of ASD reached ADI-R algorithm cutoffs in the 3 domains of impaired reciprocal social interaction, communication, and repetitive behaviors and stereotyped patterns, although failure to reach cutoff in 1 of the domains by 1 point was permitted (**Table 1**).

Current symptoms were assessed using the Autism Diagnostic Observation Schedule²⁹ and were not used as an inclusion criterion. Overall intellectual ability was assessed using the Wechsler Abbreviated Scale of Intelligence.³⁰ All participants fell within the high-functioning range on the spectrum defined by a full-scale IQ greater than 70. All participants gave informed written consent in accordance with ethics approval by the National Research Ethics Committee, Suffolk, England.

MAGNETIC RESONANCE IMAGING DATA ACQUISITION

All participants were scanned with contemporary magnetic resonance imaging (MRI) scanners operating at 3T and fitted with

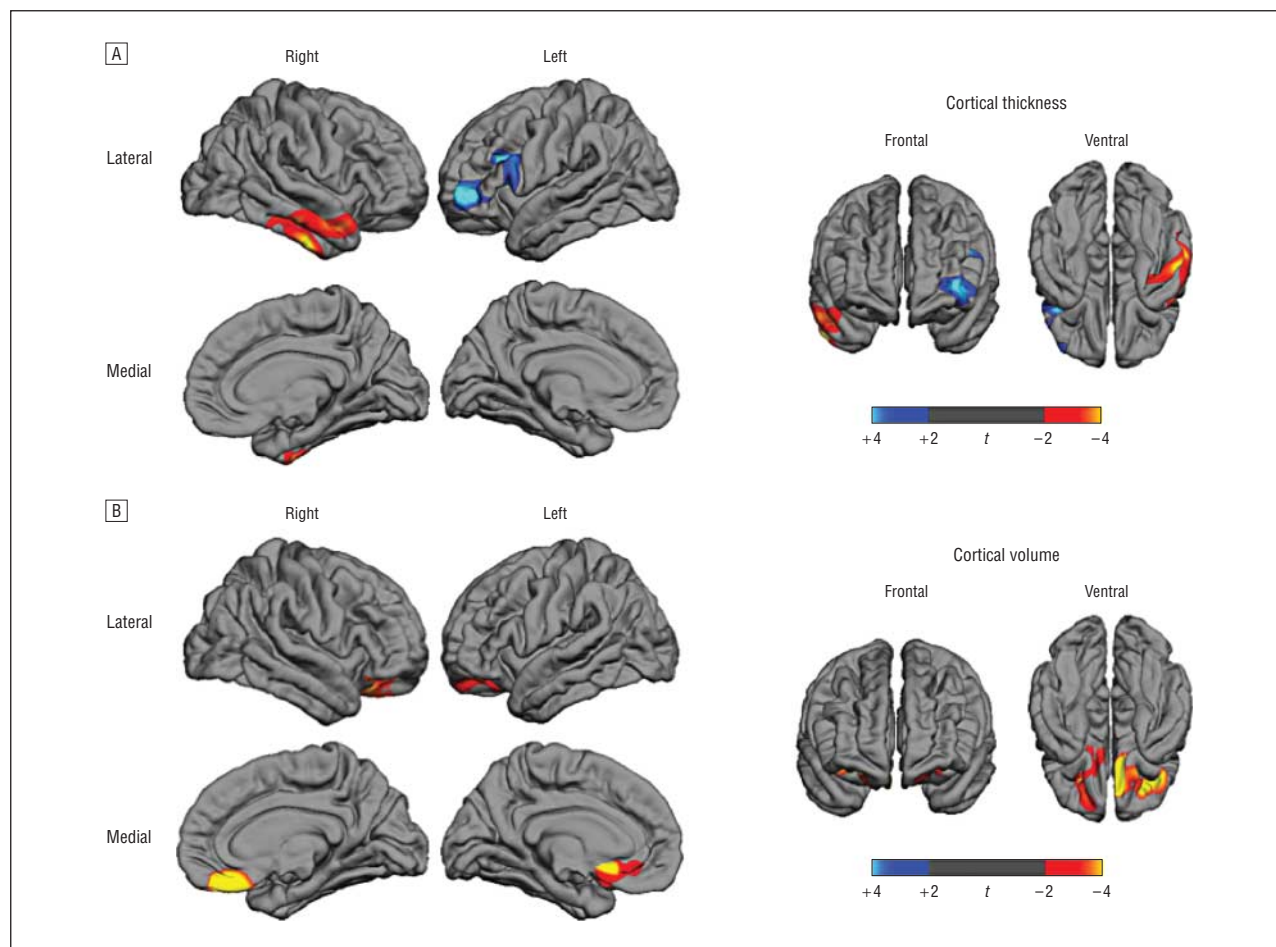


Figure 1. Random-field theory-based cluster-corrected ($P < .05$) maps for cortical thickness (A) and cortical volume (B). Relative deficits in adults with autism spectrum disorder compared with controls are displayed in red/yellow, while excesses are displayed in blue/cyan. There were no clusters of significant differences for surface area.

an 8-channel receive-only head coil (GE Medical Systems HDx at the Autism Research Centre, University of Cambridge and the Institute of Psychiatry, King's College London; Siemens Medical Systems Trim Trio at the Autism Research Group, University of Oxford). A specialized acquisition protocol with quantitative imaging (driven-equilibrium single-pulse estimation of T1) was used to ensure standardization of structural MRI scans across the 3 scanner platforms. This protocol has been validated and is described elsewhere³¹ (eAppendix, eReferences, and eFigure, <http://www.jamapsych.com>).

IMAGE PROCESSING

Scans were initially screened by a radiologist to exclude clinically significant abnormalities and to assess the existence of movement. Scans of insufficient quality were excluded from the analysis. Brain anatomy of the data has already been investigated with another approach in a previous study.³² As the present analysis requires an advanced quality standard, 9% of the recently used MRI scans had to be rejected as being not sufficiently applicable for the procedure.

The FreeSurfer analysis suite (<http://surfer.nmr.mgh.harvard.edu/>) was used to derive models of the cortical surface in each T1-weighted image. These well-validated and fully automated procedures have been extensively described elsewhere.³³⁻³⁹ In brief, a single filled white matter volume was generated for each hemisphere after intensity normalization, skull stripping, and image segmentation using a connected components algo-

rithm.³³ Then, a surface tessellation was generated for each white matter volume by fitting a deformable template. This resulted in a triangular cortical mesh for gray and white matter surfaces consisting of approximately 150 000 vertices (ie, points of triangles) per hemisphere.

Measures of CT are the closest distance from the gray and white matter boundary to the gray matter and cerebrospinal fluid boundary at each vertex on the tessellated surface.³⁵ Vertex-based estimates of SA were obtained by computing the average of the area of the triangles incident to that vertex (ie, sharing that vertex) in a standardized, spherical atlas-space surface tessellation when mapped into the individual subject space (eAppendix, eReferences, and eFigure). This provides point-by-point estimates of the relative areal expansion or compression of each location in atlas space.^{40,41} Here, the local SA was used interchangeably with areal expansion or compression. Estimates of regional CV were derived by multiplying CT measures by their areal expansion or compression at each vertex. These measures are thus different from conventional measures of brain volume resulting from the standard FreeSurfer pipeline, and they indicate the degree of volumetric expansion or compression at each vertex. To improve the ability to detect population changes, each parameter was smoothed using a 15-mm surface-based smoothing kernel.

Group differences in total brain volume, gray matter volume, mean CT, and SA as estimated by FreeSurfer⁴² were assessed using *t* tests for independent samples.

STATISTICAL ANALYSIS

Statistical analysis was conducted using the SurfStat toolbox (<http://www.math.mcgill.ca/keith/surfstat/>) for Matlab (R2010b; MathWorks). Parameter estimates for each measure (CV, CT, and SA) and the main effect of group (G_i) were estimated by regression of a general linear model at each vertex i and subject j , with center (C_i) as a categorical fixed-effects factor and age, IQ, and a total brain measure (indicated by B_i : total brain volume for CV, mean CT for CT, and total SA for SA) as continuous covariates: $y_{ij} = \beta_0 + \beta_1 G_i + \beta_2 C_i + \beta_3 \text{Age}_i + \beta_4 \text{IQ}_i + \beta_5 B_i + \varepsilon_{ij}$, where ε is the residual error. Between-group differences were estimated from the fixed-effect coefficient β_1 normalized by the corresponding standard error. Corrections for multiple comparisons across the whole brain were performed using random-field theory-based cluster-corrected analysis⁴³ for nonisotropic images using a $P < .05$ (2-tailed) cluster significance threshold.

To explore the wider neural systems underlying ASD and to investigate the degree of spatial overlap for the 3 different measures, we reexamined between-group differences heuristically using an uncorrected threshold of $P < .05$ with a cluster threshold of 50 vertices using the same model(s) as described earlier. This resulted in spatially distributed binary patterns of differences unique to CT and/or SA, as well as their overlap, regardless of the sign (ie, based on their statistical threshold). First, a χ^2 test was used to compare frequencies of unique or overlapping differences in each morphometric parameter (ie, contingency tables), testing the null hypothesis that differences in CT and SA are equally distributed. Second, a simulation strategy was used to assess whether the observed degree of overlap between differences in CT and SA is consistent with the idea of 2 spatially independent patterns. This hypothesis was tested on the basis of $N = 10\,000$ randomly generated difference maps (ie, maps containing random t values, thresholded at $P < .05$) for CT and SA. The extent of overlap (ie, number of vertices with differences in CT and SA) was then assessed in each of the 10 000 overlapping patterns to derive a probability value of obtaining a given percentage of overlap on the basis of randomly varying patterns of differences.

CORRELATIONS BETWEEN MEASURES OF SURFACE ANATOMY AND AUTISTIC SYMPTOMS

The relationships between regional anatomical abnormalities and domains of symptom severity were explored using Pearson correlation coefficients. Within the ASD group, we examined correlations between volumetric features (ie, mean CT and CV) within and of clusters showing a significant between-group difference and the 3 domains of the ADI-R measuring symptoms at ages 4 to 5 years as well as the total Autism Diagnostic Observation Schedule scores of current symptoms.

RESULTS

Participant demographic characteristics and global brain measures are shown in Table 1. There were no differences (2-tailed) between people with ASD and controls in age ($t_{166} = -1.82$; $P = .07$), full-scale IQ ($t_{166} = 1.78$; $P = .07$), or verbal IQ ($t_{166} = -0.22$; $P = .82$). However, individuals with ASD had significantly lower performance IQs ($t_{166} = -3.54$; $P = .001$). There were no significant group differences in total brain volume ($t_{166} = -0.19$; $P = .84$), total SA ($t_{166} = -1.20$; $P = .23$), or mean CT ($t_{166} = -0.51$; $P = .61$). Using Levene's test for equality of

variances,⁴⁴ we found no evidence of heterogeneity of variance in total brain measures.

CLUSTERS OF SIGNIFICANT BETWEEN-GROUP DIFFERENCES IN SURFACE ANATOMY

Following correlation for multiple comparisons across the brain, individuals with ASD had significantly increased CT in a large cluster located in the left lateral prefrontal cortex ($P < .003$). This cluster had 2 peaks in the ventrolateral and rostromedial prefrontal cortex (peak Talairach coordinates: $-36, 42, 4$ and $-36, 20, 22$, respectively). In addition, individuals with ASD had significantly decreased CT of the right anterior temporal lobe ($P < .04$) including the superior, middle, and inferior temporal gyrus (**Figure 1A**).

Individuals with ASD had significantly decreased CV in a large cluster in the bilateral orbitofrontal cortex (peak Talairach coordinates, left: $-19, 44, -13$; right: $8, 36, -19$; **Figure 1B**) relative to controls ($P < .005$). We did not observe any significant cluster between-group differences in SA.

PATTERNS OF DIFFERENCES IN CT AND SA AND THEIR CONTRIBUTION TO DIFFERENCES IN CV

To examine the underlying contribution of variations in CT and SA to the observed differences in CV and to investigate the spatial overlap between CT and SA, we reexamined the difference maps heuristically using a more lenient statistical threshold of $P < .05$ (uncorrected). This resulted in spatially distributed patterns of differences indicating the wider neural systems implemented in ASD.

Overall, individuals with ASD had increased CT across the frontal lobe including the medial prefrontal cortex, the superior frontal gyrus, the dorsal and rostral lateral prefrontal cortex, and the left pars opercularis and pars triangularis area of the inferior frontal gyrus—overlapping with the Broca area (**Figure 2A**). Individuals with ASD also had thicker temporal cortices of the right posterior temporal lobe (eg, middle and superior temporal gyrus) and left angular gyrus. In contrast, individuals with ASD had lower CT bilaterally in the anterior part of the superior temporal lobe and in the parahippocampal cortex, in the right anterior fusiform gyrus and occipital cortex, and in the left subgenual anterior cingulate cortex (**Table 2**).

Individuals with ASD showed decreased SA (**Figure 2B**) of the following: (1) right dorsolateral prefrontal cortex and bilateral orbitofrontal cortex; (2) left inferior temporal gyrus and anterior cingulate; and (3) supplementary and pre-supplementary motor cortices. In contrast, the ASD group had increased SA of the temporoparietal junction including the supramarginal gyrus, the parahippocampal gyrus, and the medial superior parietal cortex (**Table 3**).

SPATIAL OVERLAP BETWEEN DIFFERENCES IN SA AND CT

Across both hemispheres, we found that the number of vertices with a significant difference in CT only was approximately equal to those with a significant difference in SA only (51% vs 45%, respectively; $\chi^2 = 0.37$; $P = .83$) (**Table 4**).

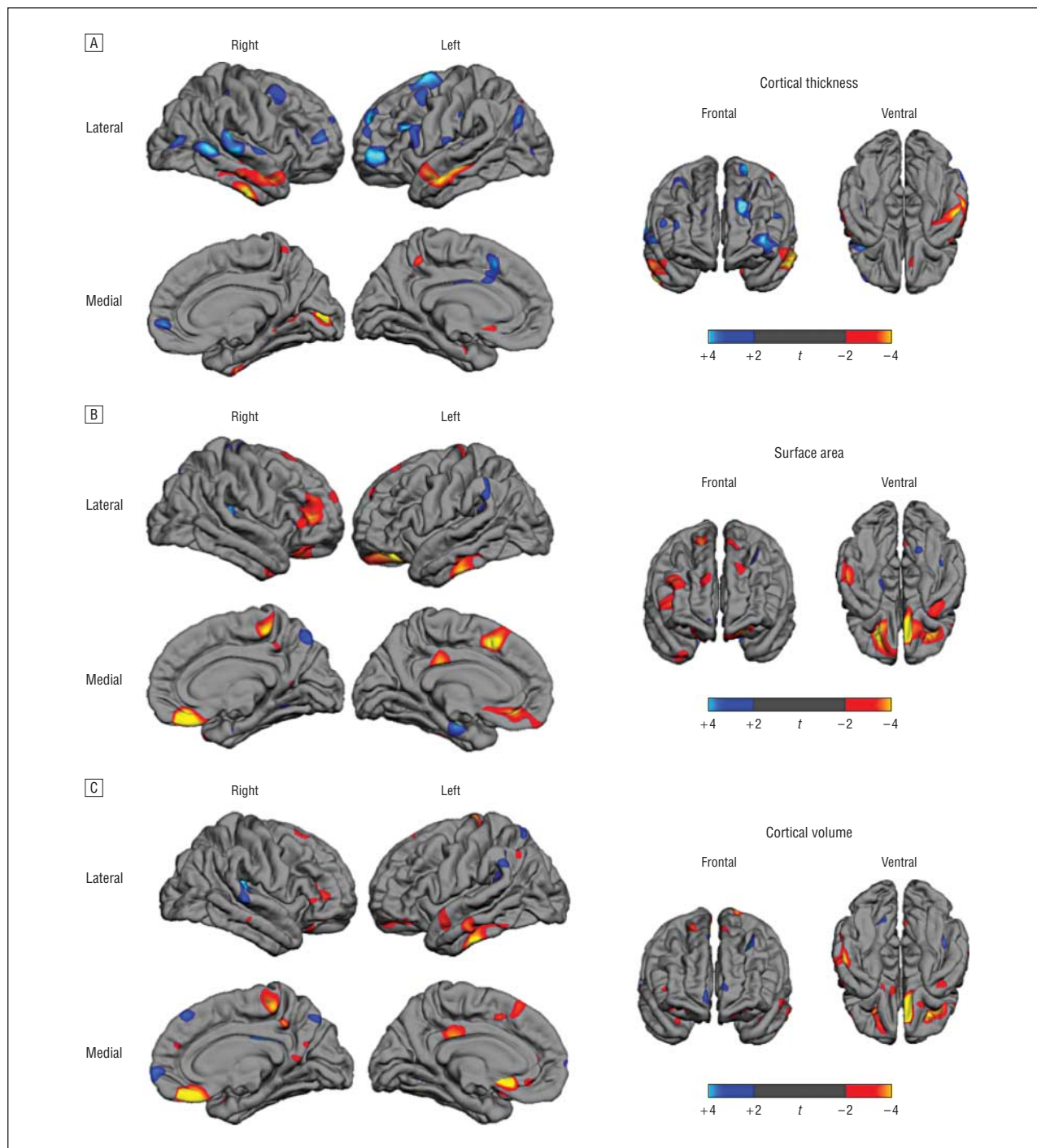


Figure 2. Spatially distributed differences in cortical thickness (A), surface area (B), and cortical volume (C) between individuals with autism spectrum disorder and controls ($P < .05$, uncorrected). Relative deficits in adults with autism spectrum disorder compared with controls are displayed in red/yellow, while excesses are displayed in blue/cyan. Surfaces are presented in lateral, medial, and frontal views for the left and right pial (outer) surface.

The patterns of significant differences in CT and SA were largely nonoverlapping and shared only about 3% of all significantly different spatial locations on the cerebral surface, ie, the probability that any 1 vertex has an overlapping difference in *both* CT and SA is very low. Simulations revealed that the probability of obtaining the same degree of overlap (ie, 3%) between 2 randomly generated difference maps is as high as 85%. The observed percentage of overlap is hence consistent with the idea

that differences in SA and CT are spatially independent and that SA and CT contribute in a unique way to the group differences in CV.

Regions with a significant group difference in SA or CT also did not overlap with regions displaying a significant association between SA and CT in general (**Figure 3**). The observed difference maps therefore coincided with regions displaying generally low coupling between SA and CT.

Table 2. Spatially Distributed Patterns of Differences in Cortical Thickness in Individuals With Autism Spectrum Disorder Compared With Controls

| Lobe | Region | Side | BA | Talairach Coordinates | | | t Value ^a |
|----------------|--------------------------|----------------|-------------------|-----------------------|--------|--------|----------------------|
| | | | | x | y | z | |
| ASD > Controls | | | | | | | |
| Frontal | Superior frontal | L | 6 | -19.70 | 0.99 | 57.33 | 2.938 |
| | | L | 32 | -9.62 | 13.86 | 43.58 | 2.749 |
| | | L | 9 | -15.95 | 43.83 | 29.03 | 3.295 |
| | Caudal middle frontal | L | 6 | -38.19 | 5.92 | 43.43 | 2.398 |
| | | R | 6 | 35.93 | 7.77 | 42.99 | 2.348 |
| | Rostral middle frontal | L | 44 | -35.64 | 20.46 | 22.51 | 2.983 |
| | | L | 10/46 | -35.60 | 42.50 | 3.78 | 3.095 |
| | Rostral middle frontal | R | 10 | 34.69 | 39.93 | 13.87 | 2.606 |
| | Pars opercularis | L | 44 | -41.83 | 17.66 | 10.75 | 2.601 |
| | Pars triangularis | R | 45 | 45.45 | 21.88 | 17.51 | 2.056 |
| Temporal | Medial orbitofrontal | R | 10 | 8.50 | 48.45 | 4.04 | 2.658 |
| | Middle temporal gyrus | R | 22 | 55.89 | -44.54 | 3.11 | 3.219 |
| | Superior temporal gyrus | R | 41 | 52.94 | -33.07 | 14.73 | 3.182 |
| Parietal | Inferior parietal | L | 39 | -40.78 | -69.60 | 26.70 | 2.636 |
| | Supramarginal gyrus | R | 40 | 33.53 | -32.68 | 44.06 | 2.286 |
| Occipital | Superior parietal | L | 2 | -47.83 | -24.44 | 28.97 | 2.743 |
| | | R | 7 | 22.89 | -57.48 | 28.77 | 2.092 |
| | | L | 19 | -37.91 | -78.33 | 2.30 | 2.313 |
| | | R | 19 | 42.92 | -72.33 | 8.68 | 2.562 |
| | | Other | Postcentral gyrus | R | 4 | 35.52 | -20.97 |
| Other | Posterior cingulate | L | 43 | -54.03 | -11.13 | 13.36 | 3.147 |
| | | L | 23 | -3.79 | -10.03 | 27.57 | 2.393 |
| | | ASD < Controls | | | | | |
| Frontal | Anterior cingulate | L | 24 | -5.27 | 8.67 | -1.19 | -2.349 |
| | Medial prefrontal cortex | R | 32 | 9.57 | 30.44 | -9.57 | -2.244 |
| | | R | 6 | 17.94 | -11.19 | 49.66 | -2.477 |
| Temporal | Middle temporal gyrus | L | 21 | -55.30 | -8.58 | -14.43 | -3.003 |
| | | R | 21 | 53.24 | -26.77 | -9.31 | -2.912 |
| | Inferior temporal gyrus | R | 20 | 49.73 | -16.06 | -22.21 | -3.060 |
| Parietal | Parahippocampal gyrus | L | 28 | -23.37 | -12.27 | -19.14 | -2.331 |
| | Superior parietal | L | 7 | -17.92 | -69.22 | 35.48 | -2.387 |
| | | R | 7 | 5.60 | -48.47 | 54.20 | -2.133 |
| Occipital | Supramarginal gyrus | L | 40 | -49.55 | -37.63 | 39.00 | -2.227 |
| | Precuneus | L | 31 | -8.81 | -46.31 | 42.66 | -2.409 |
| | Pericalcarine fissure | R | 18 | 12.89 | -78.77 | 3.94 | -3.578 |
| | Lingual gyrus | R | 18 | 17.48 | -55.98 | 2.47 | -2.883 |

Abbreviations: ASD, autism spectrum disorder; BA, Brodmann area; L, left hemisphere; R, right hemisphere.

^aThe t value at which the test statistic is significant at $P < .05$ (uncorrected).

Nevertheless, some regions showed significant abnormalities in both CT and SA (**Figure 4A**). These included the left hemisphere superior frontal gyrus, right medial orbitofrontal cortex, left medial frontal cortex, and right hemisphere ventrolateral prefrontal cortex. Within these regions, measures of CT and SA were also not correlated (all $P > .20$) and hence uniquely contributed to measures of CV (see scatterplots in Figure 4B-E).

CONTRIBUTION OF SA AND CT TO DIFFERENCES IN REGIONAL CV

Of all the underlying differences in CV ($P < .05$, uncorrected) (Figure 2C), a total of 67% were modulated by (ie, overlapped with) significant differences in CT only (8%), SA only (56%), or both CT and SA (5%) (**Table 5**). Thus, differences in SA explained a significantly larger proportion of differences in CV than did differences in

CT ($\chi^2 = 46$; $P < .001$). The remaining 31% of all significant differences in CV could not be explained by significant differences in either SA or CT and must therefore be due to a combination of subthreshold differences in CT or SA (ie, $P > .05$, uncorrected).

CORRELATION BETWEEN BEHAVIORAL VARIATION AND BRAIN ANATOMY

Within the ASD group, there were significant positive correlations between the left dorsolateral frontal cluster, where individuals with ASD displayed a significant increase in CT, and higher scores on the ADI-R communication ($r = 0.23$; $P = .02$) and repetitive ($r = 0.26$; $P = .009$) domains as well as the total ADI-R scores ($r = 0.25$; $P = .01$). We also observed a marginally significant correlation between differences in CT of the left temporal lobe and ADI-R symptoms in the repetitive domain ($r = 0.18$; $P = .47$) (**Table 6**).

Table 3. Spatially Distributed Patterns of Differences in Surface Area in Individuals With Autism Spectrum Disorder Compared With Controls

| | | | | Talairach Coordinates | | | |
|----------------|-------------------------|------|-----|-----------------------|-------|-------|----------------------|
| Lobe | Region | Side | BA | x | y | z | t Value ^a |
| ASD > Controls | | | | | | | |
| Frontal | Caudal middle frontal | L | 8 | -30.7 | 22.3 | 37.6 | 2.410 |
| Temporal | Parahippocampal gyrus | L | 28 | -22.2 | -17.5 | -21.0 | 2.751 |
| | | R | 28 | 25.6 | -10.5 | -25.1 | 2.331 |
| | Superior temporal gyrus | L | 13 | -48.2 | -41.3 | 20.2 | 2.318 |
| | | R | 13 | 37.5 | -30.8 | 13.1 | 3.010 |
| Parietal | Fusiform gyrus | R | 36 | 42.3 | -37.2 | -14.3 | 2.295 |
| | Supramarginal gyrus | L | 40 | -53.8 | -42.5 | 40.4 | 2.263 |
| | Superior parietal | R | 7 | 7.0 | -66.9 | 47.6 | 2.306 |
| | Intraparietal sulcus | R | 31 | 30.5 | -67.6 | 21.2 | 2.406 |
| Occipital | Lingual gyrus | R | 19 | 19.4 | -50.5 | -4.2 | 2.116 |
| Other | Precentral gyrus | R | 3/4 | 20.8 | -17.2 | 64.5 | 2.207 |
| ASD < Controls | | | | | | | |
| Frontal | Superior frontal | L | 32 | -10.0 | 18.2 | 42.6 | -3.304 |
| | Dorsolateral prefrontal | L | 9 | -15.8 | 49.0 | 28.2 | -2.131 |
| | Lateral orbitofrontal | R | 9 | 12.4 | 57.3 | 19.3 | -2.048 |
| | | L | 47 | -20.4 | 32.8 | -11.8 | -3.126 |
| | Rostral middle frontal | R | 11 | 5.2 | 33.5 | -21.6 | -3.681 |
| | | R | 10 | 37.6 | 39.7 | 3.5 | -2.724 |
| Temporal | Superior frontal | R | 6 | 15.2 | 20.4 | 51.3 | -2.462 |
| | Fusiform gyrus | L | 20 | -54.3 | -24.7 | -24.0 | -2.814 |
| | Temporal pole | R | 28 | 38.0 | 3.5 | -30.4 | -2.286 |
| | Inferior parietal | R | 40 | 37.7 | -42.0 | 34.1 | -2.409 |
| Occipital | Precuneus | R | 31 | 10.0 | -38.8 | 41.3 | -2.489 |
| Other | Posterior cingulate | L | 23 | -4.0 | -27.0 | 30.2 | -2.704 |
| | Paracentral lobe | R | 5 | 5.1 | -31.1 | 53.4 | -2.940 |

Abbreviations: ASD, autism spectrum disorder; BA, Brodmann area; L, left hemisphere; R, right hemisphere.

^aThe t value at which the test statistic is significant at $P < .05$ (uncorrected).

Table 4. Spatial Overlap Between Differences in Cortical Thickness and Surface Area

| Measure | No. (%) ^a | | |
|------------------|----------------------|------------------|--------------------|
| | Left Hemisphere | Right Hemisphere | Across Hemispheres |
| CT only | 8989 (56.22) | 9060 (47.10) | 18 049 (51.24) |
| SA only | 6334 (39.61) | 9669 (50.27) | 16 003 (45.43) |
| Both | 666 (4.17) | 505 (2.63) | 1171 (3.32) |
| All ^b | 15 989 (100) | 19 234 (100) | 35 223 (100) |

Abbreviations: CT, cortical thickness; SA, surface area.

^aThe number indicates the number of vertices displaying significant group difference regardless of the sign.

^bAll indicates the number of vertices displaying a significant difference in either CT or SA.

In the orbitofrontal cortex, where individuals with ASD showed significant reductions in CV, we found a significant negative correlation between symptom severity on the ADI-R social domain in the left ($r = -0.23$; $P = .03$) and right ($r = -0.22$; $P = .04$) hemispheres. Thus, individuals with more severe social autistic symptoms at ages 4 to 5 years displayed significantly smaller CV of the orbitofrontal lobes.

COMMENT

To our knowledge, this is the first study to examine regional differences in CV on the basis of its 2 components,

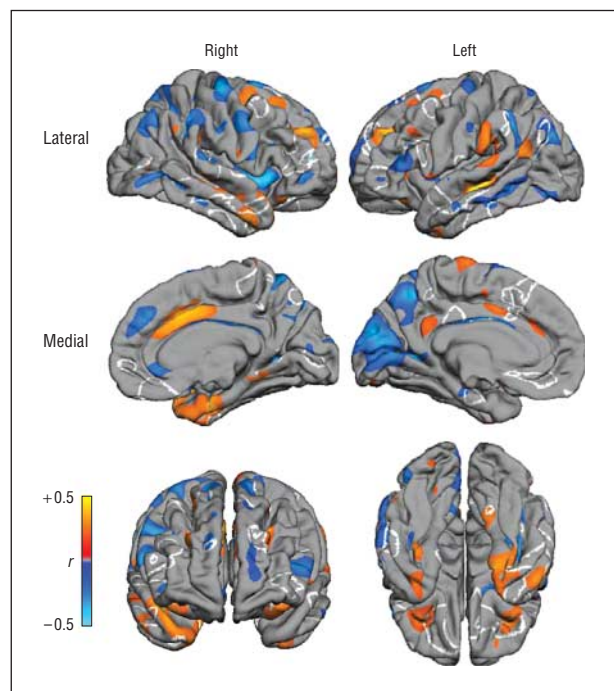


Figure 3. Significant correlations between cortical thickness and surface area in controls ($P < .01$, uncorrected). White lines indicate regions of between-group differences in surface area or cortical thickness ($P < .05$, uncorrected). Positive correlations are displayed in red/yellow, while negative correlations are displayed in blue/cyan.

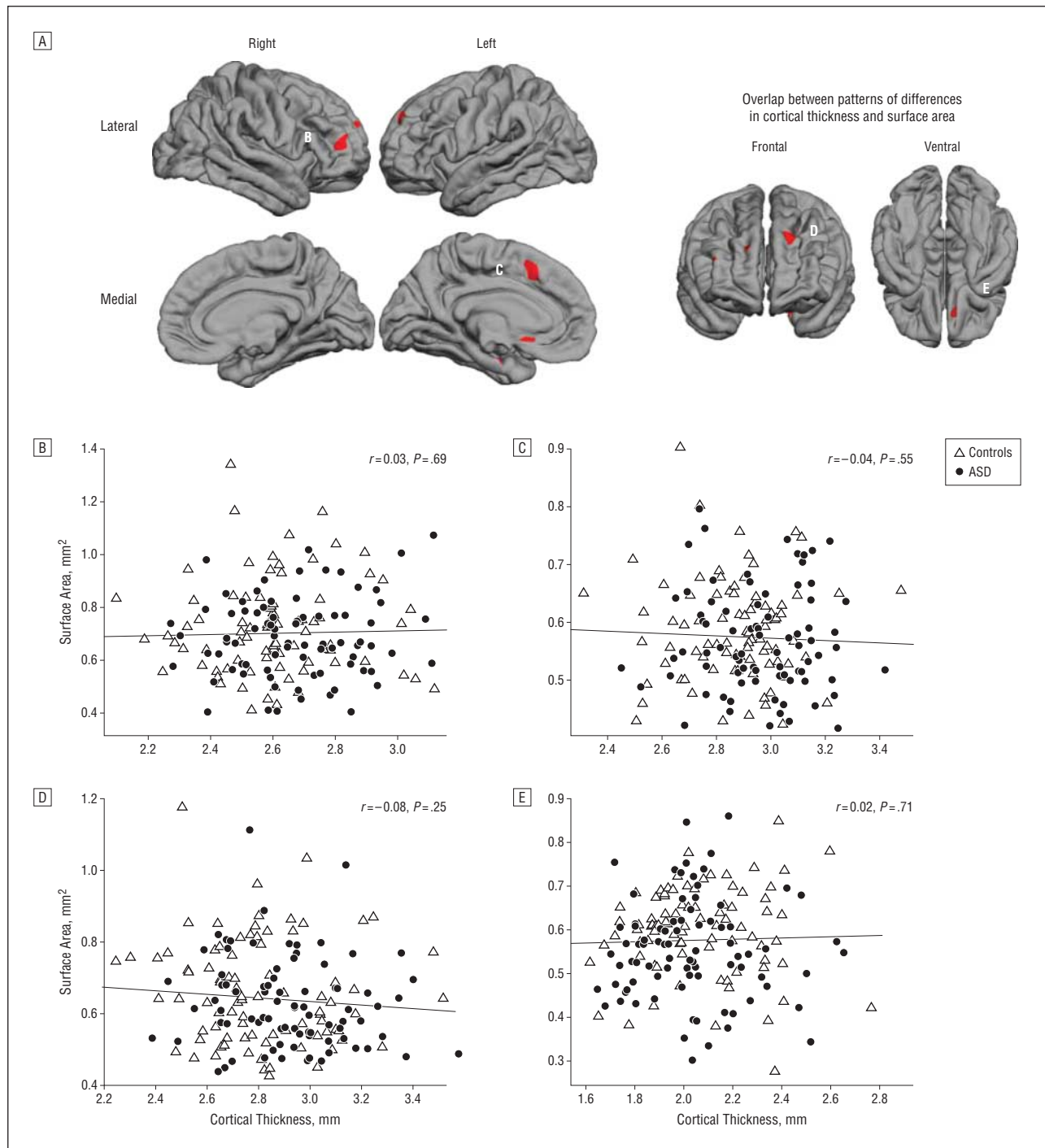


Figure 4. Overlap between patterns of differences in cortical thickness and surface area (A), with letters indicating the regions with uncorrelated measures of cortical thickness and surface area as shown in the scatterplots (B-E). ASD indicates autism spectrum disorder.

CT and SA, in a large and well-characterized sample of men with ASD. We found that individuals with ASD had significant differences in CT and CV, which primarily affected the frontal and temporal lobes. These differences were caused by subtle (ie, subthreshold) variations in CT and SA that were largely nonoverlapping. Furthermore, these spatially independent patterns of differences did not coincide with regions displaying significant associations between SA and CT, but instead overlapped with areas of generally low coupling

between them. Differences in CV observed in adults with ASD may therefore be underpinned by separable variations in its 2 components, CT and SA, which reflect variations in 2 independent neuroanatomical measures. This is of importance because CT and SA result from distinct developmental pathways that are likely modulated by different neurobiological mechanisms. This finding may provide novel targets for future studies into the etiology of the condition and a new way to fractionate the disorder.

Research agrees that ASD is a highly heterogeneous condition with multiple causes (ie, complex genetics⁴⁵) and various phenotypes, which makes the neuroanatomy of ASD inherently difficult to describe. Although several autistic core structures have been highlighted by previous studies, growing evidence suggests that ASD is a neural systems condition characterized by subtle differences in large-scale neural systems rather than isolated regions with large effects.³² Herein, we first demonstrated that individuals with ASD have significant differences in CT and CV—mainly located in frontal and temporal regions—that significantly correlated with measures of symptom severity. However, these clusters of significant between-group differences were caused by subtle and spatially distributed variations in CT and SA. Our results therefore agree with the notion that the neuroanatomy of ASD is not confined to individual brain regions but rather affects wider neural systems, which may be difficult to detect using mass-univariate techniques (also see the article by Ecker et al⁴⁶).

Second, we found that the spatially distributed patterns of differences in CT and SA displayed statistically independent sources of variability (ie, were largely nonoverlapping) and thus potentially reflect different neuropathological processes. In terms of phylogeny, it is now widely believed that CT and SA originate from different types of progenitor cells, which divide in the ventricular zone to produce glial cells and neurons. Cortical thickness has been related primarily to intermediate progenitor cells (neurogenic transient amplifying cells in the developing cerebral cortex),⁴⁷ which divide symmetrically at basal (nonsurface) positions of the ventricular surface and only produce neurons.^{48,49} These neurons then migrate along radial glial fibers to form ontogenetic columns (ie, radial units). According to the radial unit hypothesis,¹⁴ CT depends on the neuronal output from each radial unit—amplified by intermediate progenitor cells—and therefore reflects the number of neurons produced in each unit. On the other hand, SA has mainly been related to radial unit progenitor cells, which divide at the apical (ventricular) surface. The early proliferation of radial unit progenitor cells leads to an increase in the number of proliferation units, which in turn results in an increase in SA.⁴⁷ In other words, SA is related to the number of ontogenetic columns. Therefore, the spatially distributed nonoverlapping patterns of differences in CT and SA in adults with ASD most likely reflect the end result of different phylogenetic processes and particularly affect frontal and temporal regions.

The existence of distinct phylogenetic processes for CT and SA also implies that at least 2 different genetic (or other) mechanisms may be involved in their etiology and regulation. The genetic dissociation of CT and SA has previously been explored in both animal and human studies. For instance, in the mouse, mutation of the genes *PAX6*, *LRP6*, and *NGN1/2* modifies the abundance of intermediate progenitor cells and results in parallel increases in CT but not SA.⁵⁰ In humans, mutations in *PAX6*⁵¹ or *TBR2*⁵² are associated with a reduction in CT relative to SA. In contrast, SA but not CT is modulated by variations in *MECP2* within specific cortical regions (eg, cuneus, fusiform gyrus).⁵⁰ A direct link be-

Table 5. Relative Contribution of Differences in Cortical Thickness and Surface Area to Differences in Cortical Volume

| Measure | No. (%) ^a | | |
|------------------|----------------------|------------------|--------------------|
| | Left Hemisphere | Right Hemisphere | Across Hemispheres |
| CT only | 529 (8.14) | 664 (7.72) | 1193 (7.90) |
| SA only | 336 (5.17) | 5120 (59.49) | 8486 (56.18) |
| Both | 155 (2.38) | 315 (3.66) | 470 (4.63) |
| All ^b | 4050 (62.31) | 6099 (70.87) | 10 149 (67.19) |
| CV | 6500 (100) | 8606 (100) | 15 106 (100) |

Abbreviations: CT, cortical thickness; CV, cortical volume; SA, surface area.

^aThe number indicates the number of vertices displaying significant group difference regardless of the sign.

^bAll indicates the number of vertices displaying a significant difference in either CT or SA.

tween these genes and the neuroanatomical phenotype of ASD remains to be established; however, there is preliminary evidence that some of these genes are associated with ASD.⁵³⁻⁵⁵ The spatially distributed pattern of differences for CT and SA may therefore reflect distinct genetic etiologies—as ASD is a neurodevelopmental disorder—and offer new targets for further exploration of the genetic mechanisms leading to ASD. Future studies of cortical anatomy in ASD will therefore need to measure more than CV alone to identify the potentially different etiological factors leading to ASD. In addition, this study highlights the need for future histological studies to identify the specific cytoarchitectonic correlates of ASD as these are not directly accessible using MRI.

We further observed that most differences in CV (67%) were driven by differences in SA rather than CT. This finding agrees with previous studies demonstrating that interindividual variation in brain volume in healthy adults is driven predominantly by differences in SA.⁵⁶⁻⁵⁸ Further, Hazlett et al²⁵ recently reported that brain enlargement observed in toddlers with ASD may be associated with increased SA but not CT. However, as SA is a 2-dimensional measure (ie, millimeters squared) and CT is a 1-dimensional measure (ie, millimeters), differences in SA will naturally have a stronger impact on measures of CV. This implies that measures of brain volume are generally more similar to measures of SA and that CT should be explored in isolation. Thus, while our study suggests that differences in brain volume in ASD may primarily be caused by differences in SA, individuals with ASD also have significant differences in CT. These may be more difficult to measure in individuals with ASD as the delineation between the gray and white matter boundary is more difficult owing to the presence of supernumerary neurons beneath the cortical plate.⁵⁹ Another factor that may influence differences in CT and SA is gyrification (ie, cortical folding). In heavily folded brain areas, vertex-based measures of cortical expansion may be decreased as more vertices are needed to describe the more complex regional geometry. In addition, increased gyrification has been associated with increased CT.^{60,61} Thus, future studies are needed to establish the relationship between volumetric measures and gyrification in ASD.

Table 6. Correlation Coefficients Between Cortical Thickness or Cortical Volume and Diagnostic Measures Within Clusters of Significant Between-Group Differences

| Cluster | Correlation Coefficient, <i>r</i> | | | | |
|---------------------|-----------------------------------|---------------------------|---------------------------------|-------------------|------------------------|
| | ADI-R Domain | | | | ADOS Total (n = 82) |
| | Social (n = 84) | Communication (n = 84) | Repetitive Behavior (n = 84) | Total (n = 84) | |
| Cortical thickness | | | | | |
| Left frontal | 0.13 | 0.23 ^a | 0.26 ^a | 0.25 ^a | -0.25 ^a |
| Left temporal | -0.05 | 0.01 | 0.18 ^a | 0.02 | -0.12 |
| Cortical volume | | | | | |
| Left orbitofrontal | -0.23 ^a | -0.11 | 0.08 | -0.16 | -0.02 |
| Right orbitofrontal | -0.22 ^a | -0.03 | 0.05 | -0.13 | -0.01 |

Abbreviations: ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule.

^aSignificant correlation at $P < .05$ (uncorrected).

Regional differences in CT and CV were predominantly observed in frontotemporal regions. This is consistent with prior reports suggesting that people with ASD have differences in frontal lobe neuronal integrity,⁶² function,⁶³⁻⁶⁵ anatomy,⁶⁶⁻⁶⁹ and connectivity.⁷ Furthermore, it has been suggested by some that individuals with ASD have a delay in frontal lobe maturation⁷⁰ and that abnormalities in frontal lobe development⁷¹ may underpin some of the social impairments reported in people with ASD (eg, deficits in social cognition^{72,73}). Our findings and the work of others thus suggest a high degree of neuroanatomical vulnerability in frontal regions that may be modulated by (mainly) nonoverlapping differences in *both* SA and CT. If we accept that CT and SA reflect different aspects of the neural architecture, our finding suggests that abnormalities in surface anatomy of specific frontal regions in ASD may be caused by different neuropathological processes.

The same applies for the temporal lobe, where individuals with ASD had significantly thinner cortices than controls, mainly in the middle and superior regions of the anterior temporal lobe. Gray matter differences in temporal regions have previously been reported in ASD during childhood,^{74,75} adolescence,⁶⁸ and young adulthood^{6,69} and have functionally been linked to processing of biological movement (ie, movement characteristic of living organisms), social perceptions, and theory of mind tasks,⁷⁶⁻⁷⁹ which have all been reported as affected in ASD.⁸⁰ Moreover, based on the radial unit hypothesis, an increase in frontal CT in ASD would imply supernumerary neurons within minicolumns, whereas a regional decrease of SA (eg, in the orbitofrontal cortex) may be related to fewer or narrower units. However, these conclusions remain to be validated by future histological studies as existing postmortem studies in ASD are rare and available samples are small.^{81,82} Furthermore, most postmortem studies are restricted to few and small regions of the cortex, so it is difficult to generalize findings across the brain.

Our study raises a number of methodological issues. First, we investigated neuroanatomy in a sample of high-functioning men diagnosed with the ADI-R as having ASD. As ASD is a spectrum condition, our sample therefore represents a specific subpopulation of the autistic phenotype and results might not generalize to other groups on the autism spectrum (eg, individuals with intellectual disability) or to females with the condition. Second, a mul-

ticenter design was used for MRI data acquisition to overcome single-site recruitment limitations. However, we used a recently developed acquisition protocol that standardizes structural MRI data across multiple platforms³¹ and also accounted for intersite effects in the statistical model.^{83,84} Therefore, the detected between-group differences cannot be fully explained by these limitations. Third, the data build on a previous study published recently by our group using voxel-based morphometry.³² Although both techniques lead to similar results in frontal regions, there is little overlap between results in the temporal and occipital lobes. Such discrepancies have been noted previously^{85,86} and most likely reflect different approaches to image normalization and registration, which may lead to differential spatial patterns of variance and thus to differential spatial sensitivity to a fixed effect size. Between-group tests on the basis of different volume metrics are hence conditioned by the variance and consequently yield to different patterns of results.⁸³ Also, the volumetric measures investigated in the present study were based on measures of areal expansion or compression (relative to a template) and hence do not provide absolute measures of regional brain volume. Last, to our knowledge, this is the first study investigating regional measures of cortical SA in individuals with ASD using a spatially unbiased vertex-based approach and their relationship to differences in CT. Hence, the results should be considered exploratory (ie, proof of concept), requiring future replication.

To conclude, differences in CV observed in individuals with ASD may be underpinned by CT and SA, which exhibited statistically independent sources of variability. These 2 factors are likely to be the result of distinct developmental pathways that are modulated by different neurobiological mechanisms. Both CT and SA would thus benefit from being explored in isolation to elucidate the etiology and neurobiology of ASD.

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REFERENCES

- Wing L. The autistic spectrum. *Lancet*. 1997;350(9093):1761-1766.
- Gillberg C. Autism and related behaviours. *J Intellect Disabil Res*. 1993;37(pt 4):343-372.
- Amaral DG, Schumann CM, Nordahl CW. Neuroanatomy of autism. *Trends Neurosci*. 2008;31(3):137-145.
- Toal F, Murphy DGM, Murphy KC. Autistic-spectrum disorders: lessons from neuroimaging. *Br J Psychiatry*. 2005;187:395-397.
- Courchesne E, Yeung-Courchesne R, Press GA, Hesselink JR, Jernigan TL. Hypoplasia of cerebellar vermal lobules VI and VII in autism. *N Engl J Med*. 1988;318(21):1349-1354.
- Abell F, Krams M, Ashburner J, Passingham R, Friston K, Frackowiak R, Happé F, Frith C, Frith U. The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans. *Neuroreport*. 1999;10(8):1647-1651.
- McAlonan GM, Cheung V, Cheung C, Suckling J, Lam GY, Tai KS, Yip L, Murphy DGM, Chua SE. Mapping the brain in autism: a voxel-based MRI study of volumetric differences and intercorrelations in autism. *Brain*. 2005;128(pt 2):268-276.
- Saitoh O, Karns CM, Courchesne E. Development of the hippocampal formation from 2 to 42 years: MRI evidence of smaller area dentata in autism. *Brain*. 2001;124(pt 7):1317-1324.
- Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N. Effects of age on brain volume and head circumference in autism. *Neurology*. 2002;59(2):175-183.
- Bolton PF, Griffiths PD. Association of tuberous sclerosis of temporal lobes with autism and atypical autism. *Lancet*. 1997;349(9049):392-395.
- Sears LL, Vest C, Mohamed S, Bailey J, Ranson BJ, Piven J. An MRI study of the basal ganglia in autism. *Prog Neuropsychopharmacol Biol Psychiatry*. 1999;23(4):613-624.
- McAlonan GM, Daly E, Kumari V, Critchley HD, van Amelsvoort T, Suckling J, Simons A, Sigmundsson T, Greenwood K, Russell A, Schmitz N, Happé F, Howlin P, Murphy DGM. Brain anatomy and sensorimotor gating in Asperger's syndrome. *Brain*. 2002;125(pt 7):1594-1606.
- Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, Jacobson K, Lyons MJ, Grant MD, Franz CE, Xian H, Tsuang M, Fischl B, Seidman L, Dale A, Kremen WS. Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex*. 2009;19(11):2728-2735.
- Rakic P. Defects of neuronal migration and the pathogenesis of cortical malformations. *Prog Brain Res*. 1988;73:15-37.
- Armstrong E, Schleicher A, Omran H, Curtis M, Zilles K. The ontogeny of human gyrification. *Cereb Cortex*. 1995;5(1):56-63.
- Mountcastle VB. The columnar organization of the neocortex. *Brain*. 1997;120(pt 4):701-722.
- Rakic P. A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. *Trends Neurosci*. 1995;18(9):383-388.
- Rakic P. The radial edifice of cortical architecture: from neuronal silhouettes to genetic engineering. *Brain Res Rev*. 2007;55(2):204-219.
- Mak-Fan KM, Taylor MJ, Roberts W, Lerch JP. Measures of cortical grey matter structure and development in children with autism spectrum disorder. *J Autism Dev Disord*. 2012;42(3):419-427.
- Hardan AY, Muddasani S, Vemulapalli M, Keshavan MS, Minshew NJ. An MRI study of increased cortical thickness in autism. *Am J Psychiatry*. 2006;163(7):1290-1292.
- Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H. Anatomical differences in the mirror neuron system and social cognition network in autism. *Cereb Cortex*. 2006;16(9):1276-1282.
- Scheel C, Rotarska-Jagiela A, Schilbach L, Lehnardt FG, Krug B, Vogeley K, Tepest R. Imaging derived cortical thickness reduction in high-functioning autism: key regions and temporal slope. *Neuroimage*. 2011;58(2):391-400.
- Hyde KL, Samson F, Evans AC, Mottson L. Neuroanatomical differences in brain areas implicated in perceptual and other core features of autism revealed by cortical thickness analysis and voxel-based morphometry. *Hum Brain Mapp*. 2010;31(4):556-566.
- Wallace GL, Dankner N, Kenworthy L, Giedd JN, Martin A. Age-related temporal and parietal cortical thinning in autism spectrum disorders. *Brain*. 2010;133(pt 12):3745-3754.
- Hazlett HC, Poe MD, Gerig G, Styner M, Chappell C, Smith RG, Vachet C, Piven J. Early brain overgrowth in autism associated with an increase in cortical surface area before age 2 years. *Arch Gen Psychiatry*. 2011;68(5):467-476.
- Raznahan A, Toro R, Daly E, Robertson D, Murphy C, Deeley Q, Bolton PF, Paus T, Murphy DGM. Cortical anatomy in autism spectrum disorder: an in vivo MRI study on the effect of age. *Cereb Cortex*. 2010;20(6):1332-1340.
- Chung MK, Worsley KJ, Robbins S, Paus T, Taylor J, Giedd JN, Rapoport JL, Evans AC. Deformation-based surface morphometry applied to gray matter deformation. *Neuroimage*. 2003;18(2):198-213.
- Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*. 1994;24(5):659-685.
- Lord C, Rutter M, Goode S, Heemsbergen J, Jordan H, Mawhood L, Schopler E. Autism Diagnostic Observation Schedule: a standardized observation of communicative and social behavior. *J Autism Dev Disord*. 1989;19(2):185-212.
- Wechsler D. *Wechsler Abbreviated Scale of Intelligence (WASI)*. San Antonio, TX: Harcourt Assessment; 1999.
- Deoni SCL, Williams SCR, Jezzard P, Suckling J, Murphy DGM, Jones DK. Standardized structural magnetic resonance imaging in multicentre studies using quantitative T1 and T2 imaging at 1.5 T. *Neuroimage*. 2008;40(2):662-671.
- Ecker C, Suckling J, Deoni SC, Lombardo MV, Bullmore ET, Baron-Cohen S, Catani M, Jezzard P, Barnes A, Bailey AJ, Williams SC, Murphy DGM; MRC AIMS Consortium. Brain anatomy and its relationship to behavior in adults with autism spectrum disorder: a multicenter magnetic resonance imaging study. *Arch Gen Psychiatry*. 2012;69(2):195-209.
- Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I: segmentation and surface reconstruction. *Neuroimage*. 1999;9(2):179-194.
- Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. *Neuroimage*. 1999;9(2):195-207.
- Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000;97(20):11050-11055.

36. Fischl B, van der Kouwe A, Destrieux C, Halgren E, Ségonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM. Automatically parcellating the human cerebral cortex. *Cereb Cortex*. 2004;14(1):11-22.
37. Fischl B, Salat DH, van der Kouwe AJW, Makris N, Ségonne F, Quinn BT, Dale AM. Sequence-independent segmentation of magnetic resonance images. *Neuroimage*. 2004;23(suppl 1):S69-S84.
38. Ségonne F, Dale AM, Busa E, Glessner M, Salat D, Hahn HK, Fischl B. A hybrid approach to the skull stripping problem in MRI. *Neuroimage*. 2004;22(3):1060-1075.
39. Jovicich J, Czanner S, Greve D, Haley E, van der Kouwe A, Gollub R, Kennedy D, Schmitt F, Brown G, Macfall J, Fischl B, Dale A. Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. *Neuroimage*. 2006;30(2):436-443.
40. Rimol LM, Agartz I, Djurovic S, Brown AA, Roddey JC, Kähler AK, Mattingsdal M, Athanasu L, Joyner AH, Schork NJ, Halgren E, Sundet K, Melle I, Dale AM, Andreassen OA; Alzheimer's Disease Neuroimaging Initiative. Sex-dependent association of common variants of microcephaly genes with brain structure. *Proc Natl Acad Sci U S A*. 2010;107(1):384-388.
41. Palaniyappan L, Mallikarjun P, Joseph V, White TP, Liddle PF. Regional contraction of brain surface area involves three large-scale networks in schizophrenia. *Schizophr Res*. 2011;129(2-3):163-168.
42. Buckner RL, Head D, Parker J, Fotenos AF, Marcus D, Morris JC, Snyder AZ. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *Neuroimage*. 2004;23(2):724-738.
43. Worsley KJ, Andersmann M, Koulis T, MacDonald D, Evans AC. Detecting changes in nonisotropic images. *Hum Brain Mapp*. 1999;8(2-3):98-101.
44. Levene H. Robust tests for equality of variances. In: Olkin I, ed. *Contributions to Probability and Statistics: Essays in Honor of Harold Hotelling*. Palo Alto, CA: Stanford University Press; 1960:278-292.
45. Abrahams BS, Geschwind DH. Connecting genes to brain in the autism spectrum disorders. *Arch Neurol*. 2010;67(4):395-399.
46. Ecker C, Marquand A, Mourão-Miranda J, Johnston P, Daly EM, Brammer MJ, Maltezos S, Murphy CM, Robertson D, Williams SC, Murphy DGM. Describing the brain in autism in five dimensions: magnetic resonance imaging-assisted diagnosis of autism spectrum disorder using a multiparameter classification approach. *J Neurosci*. 2010;30(32):10612-10623.
47. Pontious A, Kowalczyk T, Englund C, Hevner RF. Role of intermediate progenitor cells in cerebral cortex development. *Dev Neurosci*. 2008;30(1-3):24-32.
48. Miyata T, Kawaguchi A, Saito K, Kawano M, Muto T, Ogawa M. Asymmetric production of surface-dividing and non-surface-dividing cortical progenitor cells. *Development*. 2004;131(13):3133-3145.
49. Noctor SC, Martínez-Cerdeño V, Ivic L, Kriegstein AR. Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. *Nat Neurosci*. 2004;7(2):136-144.
50. Joyner AH, J CR, Bloss CS, Bakken TE, Rimol LM, Melle I, Agartz I, Djurovic S, Topol EJ, Schork NJ, Andreassen OA, Dale AM. A common MECP2 haplotype associates with reduced cortical surface area in humans in two independent populations. *Proc Natl Acad Sci U S A*. 2009;106(36):15483-15488.
51. Glaser T, Jeepeal L, Edwards JG, Young SR, Favor J, Maas RL. PAX6 gene dosage effect in a family with congenital cataracts, aniridia, anophthalmia and central nervous system defects. *Nat Genet*. 1994;7(4):463-471.
52. Baala L, Briault S, Etchevers HC, Laumonnier F, Natiq A, Amiel J, Boddaert N, Picard C, Sbitti A, Asermouh A, Attié-Bitach T, Encha-Razavi F, Munnich A, Seifiani A, Lyonnet S. Homozygous silencing of T-box transcription factor EOMES leads to microcephaly with polymicrogyria and corpus callosum agenesis. *Nat Genet*. 2007;39(4):454-456.
53. Loat CS, Curran S, Lewis CM, Duvall J, Geschwind D, Bolton P, Craig IW. Methyl-CpG-binding protein 2 polymorphisms and vulnerability to autism. *Genes Brain Behav*. 2008;7(7):754-760.
54. Sultana R, Yu C-E, Yu J, Munson J, Chen D, Hua W, Estes A, Cortes F, de la Barra F, Yu D, Haider ST, Trask BJ, Green ED, Raskind WH, Distèche CM, Wijsman E, Dawson G, Storm DR, Schellenberg GD, Villacres EC. Identification of a novel gene on chromosome 7q11.2 interrupted by a translocation breakpoint in a pair of autistic twins. *Genomics*. 2002;80(2):129-134.
55. Bedogni F, Hodge RD, Nelson BR, Frederick EA, Shiba N, Daza RA, Hevner RF. Autism susceptibility candidate 2 (*Auts2*) encodes a nuclear protein expressed in developing brain regions implicated in autism neuropathology. *Gene Expr Patterns*. 2010;10(1):9-15.
56. Pakkenberg B, Gundersen HJ. Neocortical neuron number in humans: effect of sex and age. *J Comp Neurol*. 1997;384(2):312-320.
57. Filimonoff IN. The claustrum, its origin and development. *J Hirnforsch*. 1966;8(5):503-528.
58. Sanides F, Hoffmann J. Cyto- and myeloarchitecture of the visual cortex of the cat and of the surrounding integration cortices. *J Hirnforsch*. 1969;11(1):79-104.
59. Avino TA, Hutsler JJ. Abnormal cell patterning at the cortical gray-white matter boundary in autism spectrum disorders. *Brain Res*. 2010;1360:138-146.
60. Thompson PM, Lee AD, Dutton RA, Geaga JA, Hayashi KM, Eckert MA, Bellugi U, Galaburda AM, Korenberg JR, Mills DL, Toga AW, Reiss AL. Abnormal cortical complexity and thickness profiles mapped in Williams syndrome. *J Neurosci*. 2005;25(16):4146-4158.
61. White T, Hilgetag CC. Gyrification and neural connectivity in schizophrenia. *Dev Psychopathol*. 2011;23(1):339-352.
62. Murphy DGM, Critchley HD, Schmitz N, McAlonan G, Van Amelsvoort T, Robertson D, Daly E, Rowe A, Russell A, Simmons A, Murphy KC, Howlin P. Asperger syndrome: a proton magnetic resonance spectroscopy study of brain. *Arch Gen Psychiatry*. 2002;59(10):885-891.
63. Baron-Cohen S, Ring HA, Wheelwright S, Bullmore ET, Brammer MJ, Simmons A, Williams SC. Social intelligence in the normal and autistic brain: an fMRI study. *Eur J Neurosci*. 1999;11(6):1891-1898.
64. Critchley HD, Daly EM, Bullmore ET, Williams SC, Van Amelsvoort T, Robertson DM, Rowe A, Phillips M, McAlonan G, Howlin P, Murphy DG. The functional neuroanatomy of social behaviour: changes in cerebral blood flow when people with autistic disorder process facial expressions. *Brain*. 2000;123(pt 11):2203-2212.
65. Schmitz N, Daly E, Murphy D. Frontal anatomy and reaction time in autism. *Neurosci Lett*. 2007;412(1):12-17.
66. Bauman ML, Kemper TL. Neuroanatomic observations of the brain in autism: a review and future directions. *Int J Dev Neurosci*. 2005;23(2-3):183-187.
67. Carper RA, Courchesne E. Localized enlargement of the frontal cortex in early autism. *Biol Psychiatry*. 2005;57(2):126-133.
68. Waiter GD, Williams JHG, Murray AD, Gilchrist A, Perrett DI, Whiten A. A voxel-based investigation of brain structure in autism adolescents with autistic spectrum disorder. *Neuroimage*. 2004;22(2):619-625.
69. Rojas DC, Peterson E, Winterrowd E, Reite ML, Rogers SJ, Tregellas JR. Regional gray matter volumetric changes in autism associated with social and repetitive behavior symptoms. *BMC Psychiatry*. 2006;6:56.
70. Zilbovicius M, Garreau B, Samson Y, Remy P, Barthélémy C, Syrota A, Lelord G. Delayed maturation of the frontal cortex in childhood autism. *Am J Psychiatry*. 1995;152(2):248-252.
71. Schumann CM, Bloss CS, Barnes CC, Wideman GM, Carper RA, Akshoomoff N, Pierce K, Hagler D, Schork N, Lord C, Courchesne E. Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. *J Neurosci*. 2010;30(12):4419-4427.
72. Gallagher HL, Frith CD. Functional imaging of "theory of mind." *Trends Cogn Sci*. 2003;7(2):77-83.
73. Lombardo MV, Chakrabarti B, Bullmore ET, Sadek SA, Pasco G, Wheelwright SJ, Suckling J, Baron-Cohen S; MRC AIMS Consortium. Atypical neural self-representation in autism. *Brain*. 2010;133(pt 2):611-624.
74. Boddaert N, Chabane N, Gervais L, Good CD, Bourgeois M, Plumet M-H, Barthélémy C, Mouren M-C, Artiges E, Samson Y, Brunelle F, Frackowiak RJS, Zilbovicius M. Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study. *Neuroimage*. 2004;23(1):364-369.
75. Kwon H, Ow AW, Pedatella KE, Lotspeich LJ, Reiss AL. Voxel-based morphometry elucidates structural neuroanatomy of high-functioning autism and Asperger syndrome. *Dev Med Child Neurol*. 2004;46(11):760-764.
76. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry*. 2001;42(2):241-251.
77. Frith U. Mind blindness and the brain in autism. *Neuron*. 2001;32(6):969-979.
78. Hietanen JK, Perrett DI. Motion sensitive cells in the macaque superior temporal polysensory area: response discrimination between self-generated and externally generated pattern motion. *Behav Brain Res*. 1996;76(1-2):155-167.
79. Blakemore SJ, Decety J. From the perception of action to the understanding of intention. *Nat Rev Neurosci*. 2001;2(8):561-567.
80. Pelphrey KA, Carter EJ. Charting the typical and atypical development of the social brain. *Dev Psychopathol*. 2008;20(4):1081-1102.
81. Casanova MF, Buxhoeveden DP, Switala AE, Roy E. Neuronal density and architecture (Gray Level Index) in the brains of autistic patients. *J Child Neurol*. 2002;17(7):515-521.
82. Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, Rutter M, Lantos P. A clinicopathological study of autism. *Brain*. 1998;121(pt 5):889-905.
83. Suckling J, Barnes A, Job D, Brennan D, Lymer K, Dazzan P, Marques TR, MacKay C, McKie S, Williams SR, Williams SCR, Lawrie S, Deakin B. Power calculations for multicenter imaging studies controlled by the false discovery rate. *Hum Brain Mapp*. 2010;31(8):1183-1195.
84. Suckling J, Barnes A, Job D, Brennan D, Lymer K, Dazzan P, Marques TR, MacKay C, McKie S, Williams SR, Williams SCR, Deakin B, Lawrie S. The Neuro/PSYGRID calibration experiment: identifying sources of variance and bias in multicenter MRI studies. *Hum Brain Mapp*. 2012;33(2):373-386.
85. Voets NL, Hough MG, Douaud G, Matthews PM, James A, Winmill L, Webster P, Smith S. Evidence for abnormalities of cortical development in adolescent-onset schizophrenia. *Neuroimage*. 2008;43(4):665-675.
86. Hutton C, Draganski B, Ashburner J, Weiskopf N. A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. *Neuroimage*. 2009;48(2):371-380.